Proposed Decision Memo for Pancreas Transplants (CAG-00295R)

Decision Summary

The Centers for Medicare and Medicaid Services (CMS) proposes that the evidence is adequate to conclude that pancreas transplantation alone (PA) is reasonable and necessary for Medicare beneficiaries in the following limited circumstances:

1. PA will be limited to those facilities that are Medicare-approved for kidney transplantation (Approved centers can be found at: http://www.cms.hhs.gov/ApprovedTransplantCenters/);
2. Patients must have a diagnosis of type I diabetes:
   - The patient with diabetes must be beta cell autoantibody positive, or
   - The patient must demonstrate insulinopenia defined as a fasting C-peptide level that is less than or equal to 110% of the lower limit of normal of the laboratory's measurement method. Fasting C-peptide levels will only be considered valid with a concurrently obtained fasting glucose $\leq$225 mg/dL;
3. Patients must have a history of medically-uncontrollable labile (brittle) insulin-dependent diabetes mellitus with documented recurrent, severe, acutely life-threatening metabolic complications that require hospitalization. Aforementioned complications include frequent hypoglycemia unawareness or recurring severe ketoacidosis, or recurring severe hypoglycemic attacks;
4. Patients must have been optimally and intensively managed by an endocrinologist for at least 12 months with the most medically-recognized advanced insulin formulations and delivery systems.
5. Patients must have the emotional and mental capacity to understand the significant risks associated with surgery and to effectively manage the lifelong need for immunosuppression.
6. Patients must otherwise be a suitable candidate for transplantation.

CMS encourages public comment on this proposed decision through our website http://www.cms.hhs.gov/InfoExchange/02_publiccomments.asp#TopOfPage. We are particularly interested in comments that include evidence in addition to commentary. We are particularly interested in evidence that compares outcomes of patients with type 1 diabetes without kidney failure who undergo PA to similar patients with type 1 diabetes who are treated without transplantation. Also of interest is the maximum stage of kidney insufficiency permissible for a patient to receive a PA. During our review of the medical literature and various health plan policies, a wide range of kidney insufficiency (usually reported using the creatinine clearance) was found in the eligibility criteria for a PA. We will consider these comments and any new evidence prior to releasing our final decision.

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Proposed Decision Memo

TO: Administrative File: CAG- 00295R
Pancreas Transplants

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SUBJECT: Proposed Decision Memorandum for Pancreas Transplants
DATE: January 26, 2006

I. Proposed Decision

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II. Background[1]

On July 29, 2005, CMS began a reconsideration of the national coverage determination (NCD) on pancreas transplantation alone (PA) in patients with diabetes mellitus (diabetes) but without end-stage renal failure.

Types of Diabetes

The two main types of non-pregnancy-associated diabetes are type 1 diabetes and type 2 diabetes. Type 1 diabetes is an autoimmune disease, where the immune system attacks the insulin-producing beta cells in the pancreas and destroys them. The pancreas then produces little or no insulin. A person who has type 1 diabetes must take insulin daily to live. Type 1 diabetes accounts for about 5 to 10% of diagnosed diabetes in the United States.

Beta cell destruction can begin years before symptoms of type 1 diabetes develop. Symptoms include increased thirst and urination, constant hunger, weight loss, blurred vision, and extreme fatigue. If not diagnosed and treated with insulin, a person with type 1 diabetes can lapse into a life-threatening diabetic coma, also known as diabetic ketoacidosis.

Type 2 diabetes is the most common form of diabetes. About 90 to 95% of people with diabetes have type 2. This form of diabetes is typically associated with older age, obesity, family history of diabetes, physical inactivity, and ethnicity. The pancreas usually produces enough insulin but the body cannot use the insulin effectively, a condition called insulin resistance. After several years, insulin production decreases with a resultant build up of glucose in the blood.

Impact of Diabetes

In the U.S., an estimated 18.2 million people, 6.3% of the population has diabetes. Of those, 13 million have been diagnosed, and about 5.2 million people have not yet been diagnosed. Each year, about 1.3 million people aged 20 or older are diagnosed with diabetes.

Diabetes is widely recognized as one of the leading causes of death and disability in the United States. In 2000, it was the sixth leading cause of death. However, diabetes is likely to be underreported as the underlying cause of death on death certificates. About 65% of deaths among those with diabetes are attributed to heart disease and stroke.

Diabetes is associated with long-term complications that affect almost every part of the body. The disease often leads to blindness, heart and blood vessel disease, stroke, kidney failure, amputations, and nerve damage.

Patients with type 1 diabetes can also experience a number of other complications that can have a negative impact on their ability to manage their diabetes and on their quality of life. Some patients with type 1 diabetes experience what is commonly referred to as “brittle” or “labile” diabetes. While there is no specific definition (Haine, 2002), patients with brittle diabetes have repeated, widely fluctuating blood glucose levels. Much of the daily care for people with diabetes involves preventing blood glucose levels from going too low or too high. When blood glucose levels drop too lowa condition known as hypoglycemiaa person can become nervous, shaky, and confused. Judgment can be impaired, and if blood glucose falls too low, fainting can occur.

A person with type 1 diabetes can also become ill if blood glucose levels become too high, a condition called hyperglycemia. If severe enough, hyperglycemia can lead to ketoacidosis, which is a life-threatening condition where the body has extremely high levels of ketones in the blood due to a lack of insulin. A diabetic coma can be the result. Treatment for ketoacidosis must be administered in a hospital.

Patients with type 1 diabetes can develop hypoglycemia unawareness, a condition where the body does not respond appropriately to an abnormally and perhaps life-threateningly low level of glucose in the blood. These patients do not have symptoms of hypoglycemia and may need to arrange for 24 hour supervision by a friend or family member due to the increased risk of unconsciousness.

Diabetes Management

Healthy eating, physical activity, and taking insulin are the basic treatments for type 1 diabetes. In addition to healthy eating and physical activity, people with type 2 diabetes may require oral medication, insulin, or both to control their blood glucose levels. Blood glucose levels must be closely monitored through frequent blood glucose checking.

There are over 20 different types of insulin with varying characteristics in the United States. Patients are usually started on two injections of insulin per day of two different types of insulin. The type of insulin used is dependent on a patient's blood glucose levels. Fine-tuning of the type and dosage of insulin is guided by frequent blood glucose monitoring (ADA, 2005). Many patients with type 1 diabetes progress to three or four insulin injections per day in what is called "intensive therapy" or "optimal management." According to the American Association of Clinical Endocrinologists (AACE), intensive therapy is a comprehensive program that includes the frequent (three to four times per day) self-monitoring of blood glucose levels and a more complex and sophisticated insulin regimen using either multiple insulin injections per day or the use of an insulin pump. Therapy is individualized to the patient's diabetes profile (AACE, 2002).

Patient self-management is the most important component for the proper long-term management of diabetes; however, a diabetes management team is also important for the optimal, intensive care of the patient with type 1 diabetes. This team typically consists of an endocrinologist, a dietitian trained in diabetes education, a diabetes-trained nurse, and perhaps a pharmacist, clinical psychologist, or exercise physiologist. The patient's primary care doctor may work in conjunction with the endocrinologist (AACE, 2002) but due to the complex nature of treating a patient with an intensive insulin schedule, an endocrinologist usually leads the diabetes management team.

The goal of diabetes management is to keep blood glucose levels as close to the normal range as safely possible. A major study, the Diabetes Control and Complications Trial (DCCT), sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), showed that maintaining blood glucose levels close to normal reduces the risk of developing major complications of type 1 diabetes.

This 10-year study included 1,441 people with type 1 diabetes. The study compared the effect of two medical treatment approaches, intensive management and standard management, on the development and progression of eye, kidney, and nerve complications of diabetes. Intensive treatment aimed to keep hemoglobin A1C (HbA1C) as close to normal (6%) as possible. Hemoglobin A1C reflects average blood glucose over a two to three month period. Researchers found that study participants who maintained lower levels of blood glucose through intensive management had significantly lower rates of these complications (DCCT, 1993). More recently, a follow-up study of DCCT participants showed that the ability of intensive control to lower the complications of diabetes has persisted eight years after the trial ended (DCCT, 2003).

During the past 40 years, pancreas transplantation has been evolving as another treatment option for patients with type 1 diabetes. In pancreas transplantation, a whole or a part of the pancreas is implanted. A pancreas transplant is most commonly performed for patients with kidney disease who are to receive a kidney transplant concurrently (i.e., a simultaneous pancreas-kidney transplant (SPK)) or who will receive the pancreas transplant some time after receiving the kidney transplant (i.e., a pancreas-after-kidney transplant (PAK)). The vast majority of SPK and PAK transplantations have been, and continue to be, performed in patients with type 1 diabetes (Larsen, 2004) because these are the patients most likely to suffer from the complications of insulin-dependent diabetes (e.g., kidney failure, brittle diabetes, hypoglycemia unawareness).

A third type of pancreas transplant, commonly referred to as pancreas transplant alone (PA), is performed in patients with type 1 diabetes who do not have kidney disease severe enough to warrant a kidney transplant as well. Kidney function, as measured by creatinine clearance, is typically greater than 70 mL/min (Larsen, 2004). These patients typically receive a PA because their diabetes is not well controlled with insulin-based treatment. The most common indication for PA is frequent, severe hypoglycemia (Larsen, 2004). PA has also been suggested for patients with type 1 diabetes who have repeated episodes of ketoacidosis or hypoglycemia unawareness.

The immediate risks of pancreas transplantation include organ rejection, technical (i.e., surgical) failure, infection, and increased blood levels of insulin (dependent on the surgical technique used) while the immediate benefits can include a return to normal blood glucose levels, and independence from insulin injections. Longer term risks of pancreas transplantation consist of organ rejection, infection, kidney failure (due primarily to the immunosuppressive drugs), and cancer. Long term benefits include a return of the body’s ability to detect and counteract a low blood glucose level (Larsen, 2004).

III. History of Medicare Coverage

CMS has determined that pancreas transplantation falls within the benefit category of inpatient hospital services and physicians’ services.

On July 1, 1999, HCFA (now CMS) specified that pancreas transplants are only covered when performed simultaneously with or after a Medicare covered kidney transplant. A non-coverage policy continued for patients who have not experienced end stage renal failure secondary to diabetes.

In August 1999, HCFA (now CMS) removed the phrase “Medicare covered” from the policy.

Effective October 1, 2004, Medicare covers costs of transplantation of pancreatic islet cells, but only in the context of an NIH-sponsored clinical trial.

NCD Manual section 260.3

Nationally Covered Indications:

CMS determines that whole organ pancreas transplantation will be nationally covered by Medicare only when performed simultaneous with or after a kidney transplant. If the pancreas transplant occurs after the kidney transplant, immunosuppressive therapy will begin with the date of discharge from the inpatient stay for the pancreas transplant.

Nationally Non-covered Indications:

CMS determines that the following procedures are not considered reasonable and necessary within the meaning of section 1862(a)(1)(A) of the Social Security Act:

1. Pancreas transplantation for diabetic patients who have not experienced end-stage renal failure secondary to diabetes.
2. Transplantation of partial pancreatic tissue or islet cells (except in the context of a clinical trial (see section 260.3.1 of the NCD Manual)).

On April 6, 2004, the NCD noncoverage was appealed to the Department Appeals Board (DAB) under 42 CFR Section 426.510. On July 1, 2005, the DAB issued a ruling that the current record was not complete and adequate to support the validity of the provision excluding Medicare coverage of all PA procedures. CMS requested and received from the DAB a temporary stay of the proceedings in order to readdress the evidence under an NCD process.

IV. Timeline of Recent Activities

On July 29, 2005, CMS opened an NCD to determine whether PA is reasonable and necessary.

On August 29, 2005, Initial public comments were posted to the tracking sheet available at: http://www.cms.hhs.gov/mcd/viewpubliccomments.asp?nca_id=166.

V. FDA Status

Not Applicable.

VI. General Methodological Principles

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve net health outcomes for patients. An improved net health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix B. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

Public comment sometimes cites the published clinical evidence and gives CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum (see Appendix A).

VII. Evidence

A. Introduction:

This decision memorandum focuses on the use of PA in patients with the life-threatening complications associated with type 1 diabetes (brittle diabetes and hypoglycemia unawareness) while on optimal, intensive insulin therapy. In addition, only the use of PA in patients with type 1 diabetes but without a history of kidney failure is addressed. These patients do not need a kidney transplant and are not on immunosuppressive therapy. This is in contrast to patients who receive a pancreas transplant as part of an SPK or PAK procedure. Without a kidney transplant, patients with renal failure have a significantly higher mortality rate compared to the alternative, kidney dialysis. These patients need a kidney transplant and therefore must receive immunosuppressive treatment.

As discussed in Section VI above, CMS considers an item or service to be reasonable and necessary based on evidence of improved net health outcomes. The existing NCD does not provide a definitive rationale nor is there a decision memorandum for the reasonable and necessary determination for SPK and PAK. Upon examination of the case history, however, we believe that since kidney failure is associated with a higher mortality for patients who remain on kidney dialysis, CMS' past reasonable and necessary determination for SPK and PAK was based on acceptable patient and graft survival rates and the fact that the patient already must be on immunosuppressive treatment. CMS had reviewed published trial data, reports from the UNOS database, and a technology assessment from the former Office of Technology Assessments. This evidence demonstrated that the mortality rate of SPK and PAK was at least as good as for those patients not undergoing pancreas transplantation, and definite improvements in quality of life outcomes (decrease in hypoglycemic episodes, insulin independence). At that time, the mortality and graft survival rates of PA compared to SPK and PAK was markedly worse and this increased risk led to CMS' noncoverage of PA.

To expand coverage to PA, evidence is needed that demonstrates that the previously elevated risks for the procedure have been resolved and that outcomes of PA in patients with type I diabetes without kidney failure are better than the outcomes in similar patients with type I diabetes without kidney failure who do not undergo pancreas transplantation.

A high quality of evidence is critical to determine the net health outcome. The highest quality of clinical evidence generally comes from prospective, controlled clinical trials. Hence, in this NCD, CMS gives preference to results from controlled clinical trials that investigated morbidity and mortality in patients who were treated either with PA or with continued insulin therapy. However, we also review other published evidence from observation studies as well as the professional opinions found in position statements or in review articles. We also consider public comments and evidence submitted for our review.

One of the primary outcomes of interest for CMS is patient mortality. A definitive outcome such as patient mortality allows for a confident generalization of the available evidence to the Medicare population. This is an important consideration since most patients who receive PA are less than 65 years of age. Patient mortality also permits the assessment of both benefit and risk in one measurement, where benefit is derived from the avoidance of the complications of diabetes and risk results from the complications of the surgery and the need for life-long immunosuppressant therapy.

Patient mortality can be due to a variety of clinical causes. A subset of patient mortality that is of particular concern to CMS in this decision memorandum is operative mortality. Pancreas transplantation is a type of abdominal surgery that carries a risk of operative complications and death. Patients with diabetes who continue on insulin therapy are not exposed to this risk of operative mortality.

CMS also considered the morbidity associated with immunosuppression as an outcome. The life-long administration of immunosuppressive drugs after transplantation is required to prevent the body from rejecting the transplanted organ. Immunosuppressive drugs, however, can also have a negative impact on the patient and the transplanted organ. The risk of infection is increased. Larsen, 2004 reports that infection is the second most common cause of readmission to the hospital in the first months after transplantation as well as the most common cause of readmission over the long term. The risk of cancer is also increased with life-long immunosuppression. The most commonly reported cancers are post-transplant lymphoproliferative disease and skin cancer (Larsen, 2004). Additional side effects associated with immunosuppression include a decline in kidney function (a particular concern in a patient with diabetes), islet cell toxicity, inhibition of insulin secretion, insulin resistance, osteoporosis, hypertension (Stratta, 1999), and dyslipidemia (Larsen, 2004). With the exception of osteoporosis, all of these toxicities associated with immunosuppression can have a negative impact on the patient's cardiovascular health. This is critical since the most common cause of death in transplant patients is vascular disease (Larsen, 2004).

Graft survival rate and quality of life (QoL) are two additional outcomes that have been reported in the clinical literature. In this decision memorandum, graft survival rate was considered to be a secondary clinical outcome for pancreas transplantation because a patient can survive (with reinstatement of insulin therapy) despite the demise of the organ. This is in contrast to other types of organ transplantation, such as heart, where the demise of the organ leads to the demise of the patient. However, we did review graft survival to determine if the previously low graft survival rates associated with PA had improved.

A QoL assessment measures the physical and emotional/mental status of a patient. Relevant components of a QoL assessment for patients with diabetes can include degree of independence from insulin self-injections, freedom from frequent blood glucose monitoring, and frequency of hypoglycemia or hyperglycemia attacks. For the most part, the assessment of QoL relies on the patient's opinion and, hence, is a more subjective outcome than mortality.

B. Discussion of evidence reviewed

1. Questions

The development of an assessment in support of Medicare coverage decisions is based on the same general question for almost all requests: "Is the evidence sufficient to conclude that the application of the technology under study will improve net health outcomes for Medicare patients?"

The formulation of specific questions for the assessment recognizes that the effect of an intervention can depend substantially on how it is delivered, to whom it is applied, the alternatives with which it is being compared, and the delivery setting. In order to appraise the net health outcomes of PA in comparison with continued insulin therapy and identify any relevant patient and facility selection criteria, CMS sought to address the following question:

Is the quality of evidence adequate to draw a conclusion that PA produces a net health benefit compared to continued optimal insulin therapy in patients with type 1 diabetes who are unresponsive to intensive medical management as evidenced by recurring, severe hypoglycemic attacks or repeated episodes of ketoacidosis, or frequent hypoglycemia unawareness?

2. External technology assessments

On September 21, 2005, the Cochrane database and the NICE database were searched using the terms "pancreas transplantation," "pancreas," and "transplantation." Additionally, on October 27, 2005 the Blue Cross Blue Shield database was searched using the terms "pancreas transplantation," "pancreas," "transplantation," and "hypoglycemia." No technology assessments were found.

3. Internal technology assessments

On September 12, 2005, CMS performed a Pub Med search of the literature using the following search terms: pancreas and transplantation. The limitations used were: Human, English, Clinical Trial.

Summary of Evidence

As mentioned above, CMS looked for published evidence of controlled clinical trials comparing PA to patients who were on optimal insulin therapy. No controlled clinical trials were found that met this criterion. Two scientific articles were found, each presenting the findings from a retrospective, observational analysis of the United Network for Organ Sharing (UNOS)/International Pancreas Transplant Registry (IPTR) database that examined patient mortality in all three types of pancreas transplantation but also clearly and separately reported the results for the PA subgroup.

The United Network for Organ Sharing (UNOS) is a non-profit, scientific and educational organization that administers the nation's only Organ Procurement and Transplantation Network (OPTN), established by the U.S. Congress in 1984. Through the OPTN, UNOS collects and manages data about every transplant event occurring in the United States; facilitates the organ matching and placement process using UNOS-developed data technology and the UNOS Organ Center; and brings together medical professionals, transplant recipients and donor families to develop organ transplantation policy. UNOS was awarded the initial OPTN contract on September 30, 1986 and is the only organization to ever manage the OPTN. Through the OPTN, UNOS manages the waiting lists for transplants.

The IPTR is located at the University of Minnesota in Minneapolis. The IPTR maintains a database of all reported pancreas transplants worldwide. In cooperation with over 200 centers, the pre-transplant and post-transplant courses of nearly 24,000 patients who have received pancreas transplants are followed.

The review of these two scientific articles is presented below and in the evidence table in Appendix B. Following the review of the two scientific articles, ancillary evidence, some directly from published reports of the UNOS database, is presented.

Scientific articles

Venstrom JM, et al. Survival after pancreas transplantation in patients with diabetes and preserved kidney function. JAMA 2003;290(21):2817-23.

In Venstrom, 2003, the authors present the results of a retrospective, multicenter, observational study that analyzed data collected into the UNOS/IPTR database from January 1, 1995 to December 31, 2000. The study was stratified by type of pancreas transplantation (PA, PAK, SPK). Two cohorts were defined: patients on the waiting list who eventually received a PA, and those on the waiting list who did not receive a PA. Patients were excluded if they were on the waiting list for a multi-organ transplant other than SPK, had a serum creatinine greater than 2 mg/dL at the time of listing, or were listed for a PA but eventually received a SPK.

Unadjusted waiting list and post-transplant patient survival rates were determined and a mortality risk was calculated as the average risk for PA patients compared to patients on the waiting list for a comparable amount of time. Mortality risk was assessed for three clinically distinct time periods in the transplant group: 0-90 days, 91-365 days, and 366-1460 days.

A total of 11,572 patients were in the database, of which 6,595 received a pancreas transplant. Three hundred and seventy-eight of the 6,595 received a PA. In the PA group, 40% were men and 10% were 50 years old or older.

For the analysis of the PA subgroup, the transplant cohort contained 361 patients and the waiting list cohort contained 311 patients. The discrepancy between the 378 patients who received PA and the 361 patients included in the analysis was not explained. A comparison of the baseline characteristics for the transplant and waiting list cohorts did not identify any statistically significant differences.

The mortality risk was 2.27, 0.99, 1.70, and 1.57 for the 0-90 day, 91-365 day, 366-1460 day, and overall time periods, respectively. None of these results were statistically significant. The patient survival rate at one year was 96.5% for the PA subgroup and 97.6% for the waiting list subgroup. At four years the survival rate was 85.2% for the PA subgroup and 92.1% for the waiting list subgroup.

Gruessner RW, Sutherland DE, Gruessner AC. Mortality assessment for pancreas transplants.Am J Transplant 2004;12:2018-26.

Gruessner, 2004 conducted a retrospective, multicenter, observational study that analyzed data collected into the UNOS/IPTR database from January 1, 1995 to May 31, 2003. This was the same database used by Venstrom, 2003 but adds three more years of data. The study was stratified by type of pancreas transplantation (PA, PAK, SPK). Two cohorts were defined: patients on the waiting list for a PA, and those who received a PA. Patients were excluded if they were on the waiting list for a PA but eventually received a SPK, if they had a change in status from SPK/PAK/PA to kidney transplant alone (KTA), or if they were to be retransplanted. Patients with multiple listings at different transplant centers or who changed transplant center were counted only once. Patients re-listed were also counted only once (and all wait times were summed).

Unadjusted waiting list and post-transplant patient survival rates were determined. A mortality hazard ratio, for three clinically distinct time periods in the transplant group (0-90 days, 91-365 days, and greater than 365 days), was calculated. A second analysis of the mortality hazard ratio was performed on the subset of the database from January 1, 1995 to December 31, 2000 (to correspond with the Venstrom, 2003 analysis as shown above).

From 1995 to 2003, a total of 1207 patients were on the waiting list for PA, of which 647 received a pancreas transplant. In the waiting list cohort, 42% were men, the mean age was 38.8 years, and 8.3% of these patients were to receive a retransplant. A comparison of the baseline characteristics for the transplant and the waiting list cohorts was not reported.

The hazard ratio based on the full database (i.e., from January 1, 1995 to May 31, 2003) was 4.25, 1.72, 0.15, and 0.66 for the 0-90 day, 91-365 day, 366 on, and overall time periods, respectively. The ratios for 0-90 day and the 366 on time periods were statistically significant.

For the subset of the database that corresponded to the Venstrom, 2003 analysis (i.e., January 1, 1995 to December 31, 2000), the hazard ratio was 6.40, 2.90, 0.29, and 1.45 for the 0-90 day, 91-365 day, 366 on, and overall time periods, respectively. All of these results were statistically significant except for the overall time period.

The patient survival rate at one year was 97% for the PA subgroup and 96.6% for the waiting list subgroup. At four years the survival rate was 90.5% for the PA subgroup and 87.3% for the waiting list subgroup. These results were for the full database (i.e., from January 1, 1995 to May 31, 2003). Results for the subset of the database were not reported.

Summary of the Results

The following two tables present a summary of the patient survival and hazard ratio results of the Venstrom, 2003 and Gruessner, 2004 analyses. Of note, the patient survival rate from the Gruessner analysis was from January 1, 1995 to May 31, 2003, while for the Venstrom analysis it was from January 1, 1995 to December 31, 2000.

Table 1: Summary of the patient survival rate

Patient survival	PA (%)	Waiting list (%)
At 1 year	96.5 - 97	96.6 - 97.6
At 4 year	85.2 – 90.5	87.3 - 92.1

In table 1, the Venstrom and Gruessner analyses confirm each other for the one year patient survival results. The one year survival rate is the same for the PA and waiting list groups.

On its face, the four year results are also similar between the PA and waiting list groups. However, the Venstrom analysis found a better survival rate for the waiting list group compared to the Gruessner analysis.

Table 2: Summary of the hazard ratio (January 1, 1995 – December 31, 2000)

Time period (days)	Mortality Risk
0-90	2.27-6.40
91-365	0.99-2.90
366 on	0.29-1.70
Overall	1.45-1.57

In table 2, both analyses demonstrate a higher mortality during the first 90 days after transplantation compared to the waiting list, although only in the Gruessner analysis was the hazard ratio statistically significant. For the 91-365 day time period, the Gruessner analysis found a statistically significantly higher mortality risk in the transplantation group while the hazard ratio in the Venstrom analysis was essentially 1. For the 366+ day time period, the Gruessner analysis found a statistically significantly lower mortality in the transplantation group while in the Venstrom analysis the trend (i.e., not statistically significant) was for a higher mortality in the transplantation group. For the overall time period, both analyses show a trend for higher mortality in the transplantation group.

Ancillary evidence

Additional evidence directly from published UNOS/IPTR reports demonstrate that the total number of pancreas transplants in the U.S. as well as the number of each type of pancreas transplant has grown over the decades. As shown in Table 3, the majority of transplants performed are SPK, with PAK transplants the second most common, and PA transplants the least common.

Table 3: Number of Procedures Performed per UNOS/IPTR Report Time Period

UNOS/IPTR Report Time Period	Number of Procedures Performed		
	PA	**SPK**	**PAK**
1987 – 1994 (Gruessner, 1994)	186	2720	256
1996 – mid 1999 (Gruessner, 1999)	183	3257	455

UNOS/IPTR Report Time Period	Number of Procedures Performed		
2000 – 2004 (Gruessner, 2005)	453	3947	1149

Two commonly reported clinical outcomes used to measure the success of pancreas transplantation are patient survival at one year and pancreas graft survival at one year. As shown in Table 4, the patient survival rate at one year has been 90% or greater since 1987 regardless of type of transplant.

Table 4: One-Year Patient Survival Rate per UNOS/IPTR Report Time Period

UNOS/IPTR Report Time Period	One-Year Patient Survival Rate (%)		
	PA	**SPK**	**PAK**
1987 – 1994 (Gruessner, 1994)	90	91	91
1996 – mid 1999 (Gruessner, 1999)	97	95	95
2000 – 2004 (Gruessner, 2005)	98	95	95

Meanwhile, for the same time intervals, the early cases of primary pancreas transplantation were generally associated with a lower graft survival rate at one year for PA and PAK compared to SPK. Graft survival is defined as total freedom from insulin therapy, normal fasting blood glucose concentrations, and normal or only slightly elevated HbA1C values (Robertson, 2000). Table 5 shows the one year graft survival rates.

Table 5: One-Year Graft Survival Rate per UNOS/IPTR Report Time Period

UNOS/IPTR Report Time Period	One-Year Graft Survival Rate (%)		
	PA	**SPK**	**PAK**
	48	76	47

UNOS/IPTR Report Time Period	One-Year Graft Survival Rate (%)		
1987 – 1994 (Gruessner, 1994)			
1996 – mid 1999 (Gruessner, 1999)	72	76	84
2000 – 2004 (Gruessner, 2005)	76	85	78

The large, initial discrepancy in graft survival rates between the transplant subgroups was primarily due to a higher technical failure rate and a higher graft immunological rejection rate for PA and PAK. The lack of concordance between the high patient survival rates for PA and PAK and the lower pancreas graft survival rates is due to the relatively non-life-threatening nature of pancreatic deficiency compared to that of kidney failure. The presence of kidney failure, which is not an issue for patients in the PA and PAK subgroups, is a recognized risk factor for mortality (Larsen, 2004).

Regardless of the discrepancy in graft survival rates between the types of transplant, the graft survival rate at one year has generally improved over the decades. The main reasons offered for this improvement are advancements in the immunosuppressive regimens (especially the introduction of sirolimus, tacrolimus, and mycophenolate mofetil as maintenance immunosuppressants) and in the surgical techniques used, which have resulted in a decrease in the rejection rate and in the technical failure rate, respectively (Sutherland, 1999). Other reasons include improvements in the graft preservation techniques and in the management of post-transplant complications (Larsen, 2004).

Some longer term data for the subgroups of pancreas transplantation are available for the patient survival and graft survival outcomes. The patient survival rate at three years, while slightly lower per time period compared to the one year data (primarily for SPK and PAK), shows a similar pattern of improvement after the 1987-1994 time period as did the patient survival rate at one year.

Table 6: Three-Year Patient Survival Rate per UNOS/IPTR Report Time Period

UNOS/IPTR Report Time Period	Three-Year Patient Survival Rate (%)		
	PA	**SPK**	**PAK**
1987 – 1994 (Gruessner, 1994)	84	84	81

UNOS/IPTR Report Time Period	Three-Year Patient Survival Rate (%)		
1996 – mid 1999 (Gruessner, 1999)	97*	90*	90*
2000 – 2004 (Gruessner, 2005)	95*	90*	88*

* estimated by visual inspection of graph

The graft survival rate at three years has increased considerably for PA and PAK since 1987. For the 2000-2004 time period, the rate appears to be similar to that for SPK.

Table 7: Three-Year Graft Survival Rate per UNOS/IPTR Report Time Period

UNOS/IPTR Report Time Period	Three-Year Graft Survival Rate (%)		
	PA	**SPK**	**PAK**
1987 – 1994 (Gruessner, 1994)	29	68	31
1996 – mid 1999 (Gruessner, 1999)	50*	80*	70*
2000 – 2004 (Gruessner, 2005)	80*	70*	70*

* estimated by visual inspection of graph

The mean age of the patient at the time of transplant has been increasing over the decades for each pancreas transplantation subgroup. In the late 1980's, the mean age was 34.8 +/- 6.7 years while in the early 2000's the mean was 41.1 +/- 8.3 years (Gruessner, 2005). The majority of patients who have received a pancreas transplant to date are less than 65 years old. This is especially true for the PA subgroup, which tends to be the youngest of the three subgroups (Gruessner, 2005). A search of the UNOS/IPTR database reveals that only 0.2% of all pancreas transplantations performed from 1988 to 2005 have been in patients 65 years old or older.

Apart from the UNOS/IPTR reports, numerous studies have been performed and reported in the published medical literature regarding the effect of pancreas transplantation on the acute clinical complications associated with diabetes. A functioning pancreas transplant can eliminate hypoglycemia and hyperglycemia (Larsen, 2004). Robertson, 2000 reports that the elimination of the need for exogenous insulin, frequent blood glucose monitoring, and dietary restrictions has been associated with an improvement in the QoL. These QoL studies were conducted in patients who received an SPK; data on PA patients are not available.

In Robertson, 2000 the authors noted that successful pancreas transplantation has been shown in clinical studies to lead to normoglycemia and to improvement in HbA1C values and counter-regulatory responses to hypoglycemia for as long as up to five years post-transplantation. Combined with the results of the DCCT trial showing a beneficial effect of normoglycemia on the chronic complications of diabetes, the authors referred to an existing hypothesis that the ability of pancreas transplantation to produce normoglycemia may have the same beneficial effect on the chronic complications of diabetes. The authors also noted that no randomized clinical trials of transplantation versus intensive insulin-based management have been conducted to test the hypothesis.

No studies were found that explore how best to select patients with type 1 diabetes for PA.

4. MCAC

Not applicable.

5. Guidelines

The National Guideline Clearinghouse website was searched on September 21, 2005. Only one citation, the 2004 American Diabetes Association (ADA) guideline that is summarized in the next section of this decision memorandum, was identified.

CMS also reviewed pancreas transplant alone clinical criteria developed by other payers such as Aetna, Blue Cross/Blue Shield of North Carolina, and Highmark. Clinical criteria for Aetna include a history of extremely labile (brittle) insulin-dependent diabetes mellitus; recurrent, acute and severe metabolic and potentially life-threatening complications (hypoglycemia; or hyperglycemia; or ketoacidosis; or hypoglycemic unawareness) requiring medical attention, as documented by chart notes, frequent emergency room visits and/or hospitalizations (Aetna, 2004). Clinical criteria for Blue Cross/Blue Shield of North Carolina include documentation of severely disabling and potentially life-threatening complications due to hypoglycemia unawareness and labile diabetes that persists in spite of optimal medical management (Blue Cross/Blue Shield of North Carolina, 2004). Clinical criteria for Highmark include non-uremic insulin-dependent diabetics with severely disabling and potentially life-threatening complications due to hypoglycemia unawareness and liable diabetes persisting despite optimal medical management (Highmark, 2004).

6. Professional Society Position Statements

The ADA published a position statement in 2004 that established three patient selection criteria. According to the ADA, PA should be considered for patients with only type 1 diabetes who do not have kidney failure but who do have:

- A history of frequent, acute, and severe metabolic complications (hypoglycemia, hyperglycemia, ketoacidosis) requiring medical attention;
- Clinical and emotional problems with exogenous insulin therapy that are so severe as to be incapacitating; and
- Consistent failure of insulin-based management to prevent acute complications.

The ADA also noted that pancreas transplantation should only be performed in tertiary care facilities that have an active kidney transplant program because only such programs are adequately prepared to address the complex long-term medical and psychosocial needs of transplant patients. Accordingly, the ADA states that "program guidelines for ensuring an objective multi-disciplinary evaluation of the patient's condition and eligibility for transplantation should be established and followed."

The ADA's position on PA was based on a technical review of pancreas transplantation that was peer-reviewed, modified, and approved by the ADA Professional Practice Committee in 1999 and published in 2000 (Robertson, 2000). This review reported the history, surgical techniques, clinical results, and risk-benefit relationship of the various types of pancreas transplantation (i.e., PA, SPK, and PAK) in patients with type 1 diabetes. The report did not state the methodology used to search the literature or to select citations for inclusion in the review. The review did not provide evidence on the benefits of PA in patients with type 1 diabetes compared to patients with type 1 diabetes managed with optimal, intensive insulin therapy. Hence, this review provides more of an overview and expert consensus about the current status of pancreas transplantation rather than an evidence-based assessment of the procedure.

An online search performed on September 21, 2005 for a position statement on pancreas transplantation from the American Society of Transplantation or from the American Association of Clinical Endocrinologists was unsuccessful.

7. Comments

During the initial 30-day comment period, CMS received thirty comments with one on behalf of a professional society. All commenters are in favor of PA. Comments are available entirely at:
http://www.cms.hhs.gov/mcd/viewpubliccomments.asp?nca_id=166.

A. Comments with evidence

The DAB petitioner submitted the following resources to the DAB for consideration:

1. OPTN/SRTR 2003 Annual Report, Table 6.8, available at http://www.optn.org/AR2003/608_can_gender_pta.htm.
2. OPTN/SRTR 2003 Annual Report, Table 7.8, available at http://www.optn.org/AR2003/708_can_gender_pak.htm.
3. OPTN, Transplants in the US by State- Pancreas Transplants Report, available at http://www.optn.org.
4. OPTN, Transplants in the US by State-Kidney/Pancreas Transplants Report, available at http://www.optn.org.
5. Stratta, R.J., *Indications for Solitary Pancreas Transplantation,* available at http://www.insulinfree.com/articles/strattaindications.htm.
6. Sutherland, D.E.R., Gruessner, R.W.G., Gruessner, A.C., *Pancreas transplantation for the treatment of diabetes mellitus*, 25 World J. Surg. 487-96, 2001.
7. Aetna Clinic Policy Bulletins: Pancreas Transplantation Alone- Islet Cell Transplantation, available at http://www.aetna.com/cpb/data/PrtCPBA0601.html (last accessed October 5, 2004).
8. Electronic mail from Highmark Blue Cross Blue Shield, dated September 27, 2004.
9. Letter from Ron Shapiro, M.D. (dated October 6, 2004).
10. Gruessner, R.E.G., Sutherland, D.E.R., Gruessner, A.C., *Mortality After Pancreas Transplantation Compared with Mortality on the Pancreas* (Oral Abstract), 78 Transplantation2, 123, 2004.
11. Stratta, R.J., Review of *Immunosuppressive Usage in Pancreas Transplantation,* 13 Clin. Transplantation 1-12, 1999.
12. Sutherland, D.E.R., Stratta, R.J., Gruessner, A.C., *Pancreas Transplantation Outcome by Recipient Category Single Pancreas Verses Combined Kidney-Pancreas*, 3 Curr. Opin. Transplant. 231, 1998.
13. Paty, B.W., Lanz, K., Kendall D.M., Sutherland, D.E., Robertson, R.P., *Restored hypoglycemic counterregulation is stable in successful pancreas transplant recipients for up to 19 years after transplantation.*, PMID: 11579308, available at http://www.ncbi.nlm.nih.gov.
14. Stratta, Robert, Solitary Pancreas Transplantation, available at http://www.insulinfreetimes.org/itimesv100.htm.
15. Bartlett, S.T., Schewitzer, E.J., Johnson, L.B., Kuo, P.C., Papadimitriou, J.C., Drachenberg, C.B., Klassen, D.K., Hoehn-Saric, E.W., Weir, M.R., Imbembo, A.L., *Equivalent success of simultaneous pancreas kidney and solitary pancreas transplantation. A prospective trial of tacrolimus immunosuppression with percutaneous biopsy.*, PMID:8857849, available at http://ncbi.nlm.nih.gov.
16. Position Statement of the American Diabetes Association, January 2004.
17. Gruessner, A.C., Sutherland, D, *Pancreas transplant outcomes for US and non-US cases as reported to UNOS and IPTR as of June 2004*, 19 Clinical Transplantation 433-455 (2005).
18. Gruessner, R, Sutherland, D, Gruessner, A, *Mortality assessment for pancreas transplants, 4 American Journal of Transplantation* 2018-2026 (2004).
19. The aggrieved party statement filed on behalf of Sharon Reigh, with attachments, before the Medicare National Coverage Determination Review Board.

Of the nineteen documents submitted, thirteen were not controlled clinical trials (1-9, 11, 12, 14 and 19). Two of the nineteen documents submitted contained ancillary information and did not address the questions we are considering in this decision memo (13, 15). The remaining articles were included in the decision memo (10, 16, 17, and 18). Two documents address clinical criteria for coverage and are noted previously in the Guideline section of this decision memorandum (7, 8).

The DAB petitioner, as well as the petitioner's attorney also commented during the comment period. The attorney stated that based on current ADA guidelines and current research, the current NCD should be revised to cover PA in patients with significant acute complications, such as hypoglycemic unawareness, in patients whose complications can improve or stall significantly with PA, and in patients whose lives are significantly impaired by the burden of multiple complications and exogenous insulin therapy. The same commenter indicated that a recent review article by Angelika C. Gruessner and David E.R. Sutherland reported that "an analysis of U.S. pancreas transplants performed between 1988 and 2003 showed a progressive improvement in outcome, with pancreas transplant graft survival rates (GSRs) going from 75% at one year for 1988/1989 to 85% for 2002/2003 simultaneous pancreas-kidney (SPK) cases, from 55 to 78% for pancreas after kidney (PAK) cases, and from 45 to 77% for PTA cases."

CMS received comments from the president of the American Society of Transplant Surgeons (ASTS). The Society commented that the evidence cited in the current NCD, excluding coverage of PA, is updated by more current data that supports coverage for patients with type 1 diabetes who have hypoglycemic unawareness or certain other conditions but not renal failure. The Society suggested that the more contemporary data establishes the following:

- Outcomes have greatly improved for PA recipients due, in large part, to advances in immunosuppression therapy that reduce morbidity and enhance graft survival.
- PA has become a much more common procedure since 1995 and is no longer considered experimental or investigational.
- Patient screening practices have evolved to identify more candidates for PA, resulting in significantly greater benefits for the clinically appropriate patient population.

The commenter indicated that data from UNOS/IPTR, as of August 18, 2005, shows PA graft survival rates as of 2004 exceed the survival rates of SPK and PAK transplants at the time they were covered by the current NCD. Additionally, the commenter noted that although the number of PA procedures relative to the number of other forms of transplantation remains fairly small (approximately 100 per year), the aggregate number of PA procedures performed over time is significant. For the three years 2002, 2003, and 2004 there have been a total of 384 cases documented by the OPTN. The commenter also noted the ADA guidelines indicate the Program guidelines for ensuring an objective multidisciplinary evaluation of the patient's condition and eligibility for transplantation should be established. Finally, the commenter established that while it is noted that Medicare beneficiaries would likely benefit from coverage of PA in appropriate cases, most of the patients involved are less than 65 years of age. Those Medicare beneficiaries who are appropriate for this procedure are likely to be under 65 years of age and Medicare-eligible because they are classified as disabled. Twelve supporting articles were submitted with the ASTS comments. When reviewing submitted articles we are most interested in controlled clinical trials and studies that attempt to answer the questions we are considering. Three of the twelve articles fit the aforementioned criteria and are included in the decision memo (Venstrom, 2003; Gruessner 2004; Kendall, 1997). Five of the twelve articles contained ancillary information that did not address the questions that we are considering (Gold, 1994; White, 1983; Bolli, 1984; Kendall, 1997; Gill, 2001). Seven of the twelve articles were not controlled clinical trials (UNOS data; Kaufman, 2004; Cyer, 1994; White, 1983; Cyer, 1993; Tattersall, 1997; Gill, 2001).

CMS will respond to these recommendations in Section VIII below.

B. Comments without evidence

Pancreas Transplant Surgeons

Five transplant surgeons commented during the initial 30-day comment period. One surgeon stated that the decision to commit a patient to lifelong immunosuppression should not be taken lightly. He also commented that it is important to meet with all patients who are interested in pancreas transplantation and weigh the advantages and disadvantages on an individual basis. All surgeon commenters appeared to agree that patients who have frequent hypoglycemic episodes without warning symptoms are particularly good candidates for PA. Patients who are admitted to hospitals frequently for suffering from diabetic ketoacidosis were also noted as good candidates for PA. Another surgeon stated that the ADA deemed PA to be appropriate treatment for patients with diabetes with severe physiological complications (diabetic ketoacidosis or hypoglycemic unawareness) or with incapacitating clinical and emotional problems due to exogenous insulin. Additionally, this surgeon commented that UNOS data, recently analyzed by the Gruessner et al. at University of Minnesota suggested that isolated pancreas transplants conferred a survival advantage over diabetics waiting for pancreas allografts. Moreover, these data were an analysis of isolated pancreas transplants performed from 1998-2002 and do not reflect significant advances in the pancreas transplant seen in the last two years.

Other Pancreas Transplant Professionals

Many of the commenters in the pancreas transplant profession suggested PA can both save CMS money and resources while dramatically improving patients' quality of life.

Suggested Conditions of PA Coverage

The ADA supports pancreas transplants for patients with type 1 diabetes who have a history of frequent acute metabolic complications such as hypoglycemic unawareness; clinical and emotional problems with exogenous insulin therapy that are incapacitating; and consistent failure of insulin management to prevent complications.

The table below illustrates commenters opinions on which diabetic conditions should be considered for Medicare coverage of PA.

Condition	Number of Commenters
All Diabetes Cases	7

Condition	Number of Commenters
Pancreatitis	1
Severe Diabetes	2
Brittle Diabetes	5
Hypoglycemic Unawareness	8
Labile Diabetes	1
Total Pancreatectomy Patients	1

Note: Conditions above are referring to complications associated with patients suffering from type 1 diabetes, with the exception of commenters who believe all patients with diabetes should be considered for coverage of PA.

General Public

Commenters from the general public all suggested PA will increase quality of life by allowing patients to no longer be insulin-dependent. However, no research consisting of clinical trials was included.

While comments from the public are informative, they receive less weight if clinical evidence is not included as part of the comments. In general, these commenters contend that PA improves QoL by decreasing episodes of severe hypoglycemia or ketoacidosis. However, as discussed above, the important question is whether PA improves QoL as compared to optimal insulin therapy or if the improvement in QoL is at the risk of increased mortality.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." § 1862(a)(1)(A).

The Venstrom, 2003 analysis demonstrated that, compared to patients who continued to receive insulin therapy, PA is associated with a trend toward a higher hazard ratio[2] during both the initial 90-day post-operative period and overall. The Gruessner, 2004 analyses demonstrated a higher hazard ratio for mortality early on but a lower ratio after one year. The presumption in each study is that the patients who were on the waiting list, and those who ultimately received a PA, were unresponsive to insulin therapy. The main difference between the two studies occurred during the longer term where the Gruessner results showed a better hazard ratio for patients who received a PA. Each study demonstrated a high patient survival rate (greater than 95%) at one year for both the patients who received a PA and for those who continued to receive insulin therapy. Similarly, in each study the survival rate slipped after four years but was greater than or equal to 85% for both groups of patients. These patient survival results correspond well with the patient survival rate at one year for PA (98%) reported in the 2005 UNOS report but are a bit lower for the patient survival rate at three years (about 95%).

The Venstrom and Gruessner analyses were the only two studies found in the literature by CMS that compared the outcome of patients who received a PA with that of patients who were presumably clinically similar but who did not receive the procedure and therefore remained on insulin. However, neither study was a prospectively controlled and conducted clinical trial. The retrospective and observational nature of these analyses increased the potential for confounding and bias, which may have negatively influenced the results. For instance, it is not possible to determine from a patient's status on the OPTN transplant waiting list if they have been optimally managed with insulin. However, in spite of those limitations, the study did suggest that the patients undergoing PA have a long term survival at least as good as those who did not undergo PA.

In Gruessner, 2004, the authors stated that the Venstrom, 2003 analysis suffered from errors in the UNOS/IPTR database due to multiple listings and the uncertainty as to the status of the patient's kidney function. Gruessner, 2004 attempted to control for these errors. Despite the attempt to clean the database, the hazard ratios were similar for each time period, with the exception of the long term hazard ratio. This is perhaps not surprising since each study analyzed essentially the same database. Each study also failed to note the degree of loss-to-follow-up.

For CMS, there were some additional weaknesses in the evidence presented by both analyses. One weakness concerns the uncertainty surrounding the medical history and indication for placement on the waiting list, and eventual transplantation. This decision memorandum focuses on patients who suffer from recurrent, severe, disabling, and acutely life-threatening metabolic complications of type 1 diabetes that require hospitalization. These complications include hypoglycemia unawareness and ketoacidosis. The authors did not delineate the clinical reason why each patient was on the transplantation waiting list. Additionally, there is no information as to why some patients on the waiting list were selected for a transplant and others were not. Significant medical conditions could have existed in either group that would markedly affect the outcomes.

The duration of analysis for each study, and for the UNOS/IPTR reports, concerns CMS. The evidence clearly shows the short term impact of PA. The patient survival is good and comparable in the short-to-mid term for both the transplantation procedure and for continued insulin therapy. The continued improvement in the technical failure rate and in the immunological rejection rate support the good short-to-mid term patient survival rates seen in the Venstrom, 2003 and Gruessner, 2004 analyses; however, the operative mortality rate is not zero as demonstrated by both the Venstrom, 2003 and the Gruessner, 2004 analyses. There will always be some degree of morbidity and mortality associated with the surgical procedure and the subsequent life-long immunosuppressive treatment. The UNOS/IPTR database cannot shed light on the impact of PA on the longer term, diabetes-related complications.

A major CMS concern is the ability to generalize the evidence presented in the Venstrom, 2003 and Gruessner, 2004 analyses to the Medicare population age 65 and older. The mean age of the patients in the database analyzed was significantly less than 65 years. In fact, although the mean age has been increasing over the decades, PA is still typically performed in patients younger than 65 years. A review of the UNOS/IPTR database for PA shows only nine transplants have been performed on patients 65 years old or older since 1988. There has been a modest increase in the percentage of patients in the 50-64 age group undergoing PA. Since, by definition, PA is performed in a patient population that does not have kidney failure, a patient with type 1 diabetes but without kidney failure who is otherwise not disabled is unlikely to be a Medicare beneficiary. Hence, the majority of the evidence was not from the largest Medicare beneficiary group. Accordingly, CMS expects that it will continue to be rare for patients 65 years of age and older to be clinically eligible for a PA. Therefore, CMS would be highly concerned if patients 65 years of age and older received a PA.

In spite of these limitations of the available evidence, the UNOS/IPTR database studies do demonstrate that the high mortality and graft failure rates that were of a concern to CMS, and which led to the previous noncoverage of PA, appear to have been ameliorated. Mortality and graft survival rates are consistent among the three procedures. In addition, though the quality of evidence is not high, Venstrom 2003 and Gruessner 2004 have demonstrated that mortality from PA has improved to the point that long term survival is comparable to that for patients with type I diabetes on the PA waiting list that did not get a transplant. We believe these data are sufficient to assuage our concerns about the increased risks of the PA procedure as addressed in our previous NCD.

However, the lack of risk does not necessarily imply the need for coverage without a demonstrated benefit. Trial data do not exist on the benefits of PA in patients with type I diabetes compared to those with optimal insulin therapy. Data do exist for patients undergoing SPK or PAK that demonstrate significant improvements in QoL to include insulin independence and resolution of severe hypoglycemic and hyperglycemic episodes. We would not expect those results to differ in PA patients and thus believe the SPK/PAK QoL data can be generalized to the PA population.

In conclusion, we believe that the evidence is adequate to show that PA is reasonable and necessary in limited circumstances. Those limited circumstances include both patient and facility limitations. All current data have been collected from facilities approved by Medicare for combined kidney and pancreas transplantation. We will continue that requirement.

As discussed in Section VII.B.5., we have reviewed the eligibility criteria established by the American Diabetic Association and several health plans. These criteria are extremely limiting and we believe appropriately identify patients for PA. We will use the criteria consistent among the various guidelines which also match the UNOS waiting list criteria: Patients with type 1 diabetes must have a history of brittle insulin-dependent diabetes mellitus with documented recurrent, severe, acutely life-threatening metabolic complications that require hospitalization. This is limited to patients with frequent hypoglycemic unawareness or recurring severe ketoacidosis, or recurring severe hypoglycemia.

Three of the four guidelines we reviewed also required that patients fail at optimal medical management. We believe this to be a crucial eligibility factor. Though risks of the procedure have improved, significant risks remain. Thus, we will require prior to eligibility for PA that patients have a diagnosis of type 1 diabetes and undergo optimal, intensive medical management by an endocrinologist[3] for at least twelve months with the most advanced insulin formulations and improved delivery systems. These insulin formulations have become standard over the last 2-3 years and may better manage the patient with type I diabetes. It is unknown if patients managed with these insulins would have different results when compared to patients undergoing PA transplants. Twelve months or longer of optimal medical management was selected to allow for an adequate period of monitoring of the benefit of the selected insulin regimen using HbA1C.

CMS requires an accurate diagnosis of type I diabetes as determined by a positive beta cell autoantibody test or, lacking that, an accurate diagnosis of insulinopenia by meeting a C-peptide testing requirement, which for those without renal insufficiency is defined as a fasting C-peptide level that is less than or equal to 110 percent of the lower limit of normal of the laboratory's measurement method. Fasting C-peptide levels will only be considered valid with a concurrently obtained fasting glucose $\leq$225 mg/dL.[4]

In addition to these diabetes-specific criteria for pancreas transplantation, a patient must meet the physical and psychological (emotional and mental) eligibility criteria that UNOS and transplant programs have established. Patients should be otherwise eligible for transplantation. Patients also should be emotionally and mentally able to make an informed decision about surgery and to properly manage their health care after the transplantation.

The ability of pancreas transplantation to halt or reverse the long term complications of diabetes is unknown and continues to be debated within the professional community. Similarly, data are not available to determine whether performing pancreas transplantation earlier in the course of disease would prevent complications (Robertson, 2000). Whether or to what extent pancreas transplantation alters the course of autonomic neuropathy is still controversial (Larsen, 2004). The clinical improvement of autonomic neuropathy is known to be variable from patient to patients (Larsen, 2004), hence the magnitude of improvement may be a function of time after resumption of normoglycemia. There is some preliminary evidence that a functioning pancreas graft can improve the ability of a patient with autonomic neuropathy to recognize the symptoms of hypoglycemia and to respond appropriately (Kendall, 1997). A controlled clinical trial that focuses on this outcome needs to be conducted to confirm these preliminary results. We encourage and expect those trials to be done. We will be monitoring evidence development through trials, claims data and the UNOS database to determine the need for future modification of this proposed policy.

IX. Proposed Decision

The Centers for Medicare and Medicaid Services (CMS) proposes that the evidence is adequate to conclude that pancreas transplantation alone (PA) is reasonable and necessary for Medicare beneficiaries in the following limited circumstances:

1. PA will be limited to those facilities that are Medicare-approved for kidney transplantation (Approved centers can be found at: http://www.cms.hhs.gov/ApprovedTransplantCenters/);
2. Patients must have a diagnosis of type I diabetes:
   - The patient with diabetes must be beta cell autoantibody positive, or
   - The patient must demonstrate insulinopenia defined as a fasting C-peptide level that is less than or equal to 110% of the lower limit of normal of the laboratory's measurement method. Fasting C-peptide levels will only be considered valid with a concurrently obtained fasting glucose $\leq$225 mg/dL;
3. Patients must have a history of medically-uncontrollable labile (brittle) insulin-dependent diabetes mellitus with documented recurrent, severe, acutely life-threatening metabolic complications that require hospitalization. Aforementioned complications include frequent hypoglycemia unawareness or recurring severe ketoacidosis, or recurring severe hypoglycemic attacks;
4. Patients must have been optimally and intensively managed by an endocrinologist for at least 12 months with the most medically-recognized advanced insulin formulations and delivery systems.
5. Patients must have the emotional and mental capacity to understand the significant risks associated with surgery and to effectively manage the lifelong need for immunosuppression.
6. Patients must otherwise be a suitable candidate for transplantation.

Appendix A: General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine whether: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve net health outcomes for patients. An improved net health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

CMS divides the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the relevance of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention’s risks and benefits.

The issues presented here represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has unique methodological aspects.

1. Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to help ensure adequate numbers of patients are enrolled to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias)
- Co-interventions or provision of care apart from the intervention under evaluation (confounding)
- Differential assessment of outcome (detection bias)
- Occurrence and reporting of patients who do not complete the study (attrition bias)

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials

- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study's selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess the evidence.

2. Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens, and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease, and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing, and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage decisions for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation), and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations because one of the goals of our determination process is to assess net health outcomes. We are interested in the results of changed patient management not just altered management. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

3. Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Net health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. For most determinations, CMS evaluates whether reported benefits translate into improved net health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

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[1] Portions of the Background section are taken from the National Diabetes Information Clearinghouse, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, http://diabetes.niddk.nih.gov/dm/pubs/overview/#managed. Accessed October 14, 2005.

[2] Fletcher, Robert H. Clinical epidemiology: the essentials/Robert H. Fletcher, Suzanne W. Fletcher, Edward H. Wagner. 3rd ed. 1996 Williams & Wilkins, Baltimore, MD.

[3] The care of a patient with type 1 diabetes who is receiving intensive medical management, especially if the patient suffers from brittle diabetes or hypoglycemia unawareness, is more complex. Hence, intensive medical management is best administered by a team of health care professionals that includes a physician who is a diabetes expert due to extensive diabetes-focused training and experience.

[4] See our previous NCD on insulin pumps (Pub 100-3, Section 280.14) for information about the diagnosis of type I diabetes and delivery systems (insulin pumps).

Appendix B: Evidence Table [PDF, 196KB]
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